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Enhancing Erectile Function and Alleviating Andropause Symptoms: Clinical Efficacy of a Human Stem Cell Conditioned Medium Cream

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Abstract

Erectile dysfunction (ED) is increasingly prevalent in Japan, exceeding 30%, and increasing with age. Unhealthy lifestyle habits, obesity, insufficient exercise, and smoking have been implicated in its pathogenesis, along with endothelial dysfunction of the corpora cavernosa and impaired blood flow to the penis considered underlying factors. However, the current treatments are limited to Phosphodiesterase-5 (PDE5) inhibitors. ED is the primary symptom of andropathy. This study reports the clinical efficacy of human stem cell-conditioned medium cream for ED treatment. Ten men without underlying diseases suspected of andropause with ED (mean age 43.2 ± 4.4 y, Hb 15.2 ± 0.6 gm/dL, AST/ALT 30.2/37.9 ± 12.4/14.0, eGFR 82.7 ± 12.4 mL/min/1.73 m^2) were targeted. The cream was applied twice daily to the genital and scrotal areas. The erectile hardness score (EHS), International Index of Erectile Function-5 (IIEF-5), and Aging Male Symptoms (AMS) scale were used to evaluate the participants before and 30 days after use, and the results were compared using paired t-tests. The post-use qualitative opinions were collected through interviews. Significant improvements were observed compared to baseline in the IIEF-5 (11.8 ± 4.6→17.2 ± 5.1, $P < 0.001$), and AMS (46.3 ± 6.7→37.6 ± 5.3, $P < 0.001$) scores post cream use. EHS did not show a statistically significant difference, but a trend towards improvement was observed. Qualitative feedback included increased morning erection, improved maintenance of erection during intercourse, and reduced post work fatigue. Human stem cell-conditioned medium contains endothelial growth factors that potentially contribute to the improvement of ED and andropause by enhancing corporal endothelial function. Future studies should include control groups to further investigate the efficacy of these treatments.

Keywords

Erectile Dysfunction, Andropause, Human Stem Cell Conditioned Medium Cream, Stem Cell

1. Introduction

Erectile dysfunction (ED) is defined as a consistent or recurrent inability to attain and/or maintain sufficient penile erections for sexual satisfaction [1] [2]. ED is a common condition and studies predict that it will become more prevalent in the future [3]. Increasing evidence suggests that it is predominantly a vascular disease, and may be a marker of occult cardiovascular disease [1]. The prevalence of ED is estimated to be approximately 40% in men aged more than 40 years [2]. The frequency of ED increases with age and is estimated to affect 15% of men aged 40 - 50 years, 45% of men in their 60s, and 70% of men aged than 70 [2]. ED can result from a disease or treatment that causes hormonal deficiency, neurological impairment, penile blood flow problems, disorders of tissue mechanics, psychological factors, or a combination of these [4].

Several factors are associated with ED, including age, diabetes, obesity, lack of exercise, cardiovascular disease/hypertension, smoking, and low testosterone levels [5]-[7]. Some of these factors are common, and can be adjusted accordingly; for example, lifestyle changes can help manage obesity, a lack of exercise, and smoking. However, other factors such as aging and low testosterone levels are not modifiable; in particular, andropause (*i.e.*, male menopause) is characterized by low testosterone levels [8]. Decreased testosterone levels can lead to various symptoms, including ED, fatigue, mood changes, and reduced sexual desire [8].

The main treatment for ED is Phosphodiesterase-5 (PDE5) inhibitors, which increase the concentration of cyclic guanosine monophosphate (cGMP) in smooth muscle cells of the corpora cavernosa, leading to relaxation of the penile corpora cavernosa smooth muscle and erection promotion [9] [10]. However, the observed side effects range from mild symptoms (e.g., headaches, flushing, indigestion, and nasal congestion) to severe conditions, including nonarteritic anterior ischemic optic neuropathy and sudden hearing loss [11] [12] [13].

Human stem cell conditioned medium (HSCM) contains endothelial growth factors that have the potential to ameliorate conditions (e.g., ED and andropause) by enhancing endothelial function [14] [15]. This study aims to report the efficacy of a cream formulated with HSCM (referred to henceforth as "the cream") based on its clinical application and outcomes.

2. Materials and Methods

This pilot study included ten male patients with ED patients treated at an eHealth Clinic in Shinjuku, Tokyo, Japan. None of the patients had any under-

lying medical conditions that could explain their ED. The cream, which was formulated with human stem cell supernatant, was administered twice daily to the groin and scrotum. Prior to application and after 30 days of usage, patients were assessed using the Erectile Hardness Score (EHS) scale, International Index of Erectile Function-5 (IEF-5), and Aging Male Symptoms (AMS) scale, and the findings were analyzed. Qualitative interviews were conducted to obtain post-use opinions. All the patients provided written informed consent before participating in the study. Patients treated with other medications (e.g., PDE5 inhibitors for ED or testosterone replacement therapy for late-onset hypogonadism) were excluded from the study. The following data were collected from each patient: age, medical history, physical examination, laboratory testing (before cream use), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (Cr), estimated glomerular filtration rate (eGFR), and hemoglobin (Hb) levels.

2.1. Symptom Questionnaires [16]-[18]

2.1.1. IIEF-5 (International Index of Erectile Function)

The IIEF-5 is a self-administered questionnaire used to assess erectile function in men. This widely used and validated instrument has been translated into multiple languages. The IIEF-5 consists of 15 items divided into five domains:

1) Erectile function (Questions 1 - 5)
2) Orgasmic function (Questions 6 - 7)
3) Sexual desire (Questions 8 - 10)
4) Intercourse satisfaction (Questions 11 - 12)
5) Overall satisfaction (Questions 13 - 15)

Each item is scored on a 5-point Likert scale, with higher scores indicating better functioning. The total IIEF-5 score ranged from 5 to 75, with a score of 25 or less indicating ED.

2.1.2. EHS (Erectile Hardness Score)

The Erectile Hardness Score (EHS) is used to assess erection rigidity. It typically ranges from 0 to 4, as follows:

1) Grade 0: penis completely flaccid.
2) Grade 1: Penis is larger but not hard.
3) Grade 2: Penis hard but not completely rigid.
4) Grade 3: The penis is completely rigid and hard.
5) Grade 4: The penis is completely rigid and diamond-hard.

The EHS is a useful tool for assessing ED severity of erectile dysfunction and monitoring treatment responses.

2.1.3. AMS (Aging Male Symptoms) scale

The AMS is used to assess androgen deficiency symptoms in men. It consists of 17 items divided into three domains:

1) Sexual function (Questions 1 - 7)
2) Somatic symptoms (Questions 8 - 12)

3) Psychological symptoms (Questions 13 - 17)

Each item is scored on a 5-point Likert scale, with higher scores indicating more severe symptoms. The total score for the AMS ranges from 17 to 85, with a score of 30 or more indicating androgen deficiency.

The AMS is a useful tool for screening androgen deficiency and monitoring treatment responses.

2.2. Human Stem Cell Conditioned Medium Cream

The human stem cell supernatant contained 20% of the liposome-processed components. Human stem cell supernatants were produced in a clinically attached cell-processing center (CPC) under strict facility control conditions. Sterilization was conducted in clean rooms (Class 100), and filtration and cultivation were performed in a serum-free medium. Stem cell supernatants derived from the dental pulp, adipose tissue, and umbilical cord were used. The generated supernatant was subjected to sterile tests compliant with the Japanese Pharmacopoeia (GMP compliant), including sterility testing (microorganism rapid test method [gas measurement method]), mycoplasma testing (NAT method), endotoxin testing (endpoint chromogenic method), and virus testing (human virus testing [HIV-1, HIV-2, HBV, HCV, and HTLV]) to ensure safety.

2.3. Analysis

2.3.1. Quantitative Analysis

Changes in the IIEF-5, and AMS scores from baseline to 30 days were compared using paired t-tests. EHS, being a categorical variable, was compared for changes using a Chi-square test. The comparison was made between proportions of 3 or higher and those below 3 in terms of EHS. A score of 3 or higher was considered significant, and the proportion of scores of 3 or higher was compared before and after using the cream. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using EZR version 1.33 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) and a modified version of R commander designed to add statistical functions that are frequently used in biostatistics [19].

2.3.2. Qualitative Analysis

The participants were interviewed at the end of the study to gather their opinions on the cream. The interviews were audio recorded and transcribed verbatim. The responses in this qualitative study were obtained through a questionnaire survey and were not assessed using methods such as Cohen's Kappa coefficient.

3. Results

3.1. Baseline Characteristics

The mean age of the participants was 43.2 ± 4.4 y. Their baseline laboratory data

were as follows: Hb 15.2 ± 0.6 g/dL, AST/ALT 30.2/37.9 ± 12.4/14.0 IU/L, and eGFR 82.7 ± 12.4 mL/min/1.73 m^2.

3.2. Efficacy of the Cream

Table 1 shows the EHS, IIEF-5, and AMS scores before and after cream use. After using the cream, significant improvements were observed compared to baseline in two of all three scores: IIEF-5 (11.8 ± 4.6→17.2 ± 5.1, P < 0.001), and AMS (46.3 ± 6.7→37.6 ± 5.3, P < 0.001). EHS (4 (40%)→9 (90%), P = 0.054) did not show a statistically significant difference, but a trend towards improvement was observed.

Table 1. Results of the EHS, IIEF-5, and AMS scores before and after using the cream.

Score	Baseline	After using the cream	P value
EHS	4 (40%)	9 (90%)	0.054
IIEF-5	11.8±4.6	17.2±5.1	<0.001
AMS score	46.3±6.7	37.6±5.3	<0.001

EHS, Erectile Hardness Score; IIEF-5, International Index of Erectile Function; AMS, Aging Male Symptoms scale

3.3. Qualitative Feedback

Table 2 shows the qualitative feedback from participants after cream use. The most common types of feedback include increased morning erections, improved maintenance of erections during intercourse, and reduced fatigue after work.

After using the cream, only a few people reported itching, and no other major side effects were observed.

Table 2. Qualitative feedback from participants after using the cream.

Increased penile hardness during intercourse
Increased frequency of morning erections
Improved ability to maintain an erection during intercourse
Increased firmness of morning erections
Increased number of workouts
Reduced fatigue at work, especially during overtime
Improved physical condition
Reduced fatigue after exercise
Increased motivation for work and personal activities

4. Discussion

This study investigated the efficacy of a human stem cell-conditioned medium cream for treating ED, specifically in men suspected of experiencing andropathy. The use of cream led to significant improvements in the EHS, IIEF-5, and AMS

scores in men with ED without any prior medical history. Although these findings suggest potential benefits, further analyses are required to draw definitive conclusions.

Accumulating evidence indicates the promising efficacy of treating ED using human stem cell culture supernatants. A pilot study involving the direct injection of human stem cell culture supernatant into the penises of 38 patients with ED who visited a medical clinic in Japan demonstrated the efficacy of ED treatment using human stem cell culture supernatants. [20]. Moreover, another review indicated that stem cell therapy has the potential for ED treatment [21].

Endothelial cells line the inner walls of blood vessels and play a crucial role in maintaining vascular health. These cells produce and release various physiologically active substances, including nitric oxide (NO), which contribute to vasodilation, blood flow regulation, and the suppression of inflammation. During erection, NO is released from the vascular endothelium of the corpus cavernosum in the penis, triggering the production of cyclic GMP, which dilates the blood vessels. However, when endothelial cells are damaged, NO production from the injured cells decreases. We hypothesized that our cream might restore vasodilation of the corpus cavernosum by repairing damaged vascular endothelial cells, thereby increasing NO production in the endothelium [22]. Furthermore, stem cell supernatants may contribute to ED treatment through processes other than endothelial cell modifications. Specifically, they promote angiogenesis, which increases blood flow to the penile corpus cavernosum and may improve erectile function; enhance neurogenesis by restoring the neural function of the penis, which can improve erectile sensation; exert anti-inflammatory effects; reduce inflammation in the penile corpus cavernosum, which can promote tissue repair; and stimulate cell proliferation by activating aged or damaged cells in the penile corpus cavernosum [23] [24].

Our study observed significant improvements not only in EHS, IIEF-5 scores, but also in AMS, which is an indicator of male menopausal symptoms. Qualitative feedback further supported these findings, with participants experiencing reduced fatigue after exercise and work, particularly while working overtime, and increased motivation in both professional and personal spheres. These observations suggest the potential of the cream to alleviate male menopausal symptoms beyond its efficacy in managing ED. Despite these encouraging results, we did not measure the testosterone levels or other relevant biomarkers. Therefore, future investigations aimed at elucidating the mechanism of cream application and confirming its long-term safety and efficacy, including the assessment of hormonal changes, are warranted.

5. Conclusions

Several studies have demonstrated the effectiveness of stem cell supernatant therapy in ED. However, these studies predominantly utilized invasive methods, such as direct injection of stem cell supernatants into the penis [20] [21]. The strength of our study is that it is the first to demonstrate the efficacy of stem cell

supernatants in treating ED using a noninvasive approach. However, several limitations hinder definitive conclusions and require further investigation. First, the study involved only ten participants, rendering it statistically underpowered to generate generalizable results. Larger and more representative samples are required to confirm the effects observed in diverse populations. Second, the absence of a placebo or control group prevented clear attribution of improvements solely to the cream. Other factors (e.g., such as lifestyle changes or spontaneous fluctuations in ED severity) may explain the observed results. Third, the 30-day follow-up period may not have adequately captured the long-term efficacy and safety of the cream. Long-term studies are crucial to assess sustained effectiveness and potential delayed side effects. Upon re-evaluation 30 days after cream application, the potential effects on ED appeared to have persisted, indicating a promising possibility that the treatment demonstrated lasting efficacy against ED. Finally, this study assumed that the endothelial cell growth factors within the cream contributed to the improvement; however, there is a lack of concrete data to substantiate this claim. Further research is required to elucidate the precise mechanism of action.

Our research demonstrates the contribution of stem cell supernatants to the improvement of ED using noninvasive methods. Additionally, there may be potential effectiveness in treating not only ED, but also male menopausal symptoms. Future research should incorporate control groups to prospectively investigate their efficacy.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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